



TITLE:

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ORIGINAL ARTICLE

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Osimertinib in Japanese patients with *EGFR* T790M mutation-positive advanced non-small-cell lung cancer: AURA3 trial

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Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the first-line treatment for patients with *EGFR* mutant non-small-cell lung cancer (NSCLC). However, most patients become resistant to these drugs, so their disease progresses. Osimertinib, a third-generation EGFR-TKI that can inhibit the kinase even when the common resistance-conferring Thr790Met (T790M) mutation is present, is a promising therapeutic option for patients whose disease has progressed after first-line EGFR-TKI treatment. AURA3 was a randomized (2:1), open-label, phase III study comparing the efficacy of osimertinib (80 mg/d) with platinum-based therapy plus pemetrexed (500 mg/m²) in 419 patients with advanced NSCLC with the *EGFR* T790M mutation in whom disease had progressed after first-line EGFR-TKI treatment. This subanalysis evaluated the safety and efficacy of osimertinib specifically in 63 Japanese patients enrolled in AURA3. The primary end-point was progression-free survival (PFS) based on investigator assessment. Improvement in PFS was clinically meaningful in the osimertinib group ($n = 41$) vs the platinum-pemetrexed group ($n = 22$; hazard ratio 0.27; 95% confidence interval, 0.13-0.56). The median PFS was 12.5 and 4.3 months in the osimertinib and platinum-pemetrexed groups, respectively. Grade ≥ 3 adverse events determined to be related to treatment occurred in 5 patients (12.2%) treated with osimertinib and 12 patients

Abbreviations: AE, adverse event; CI, confidence interval; CNS, central nervous system; DCR, disease control rate; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PFS, progression-free survival; SAE, serious adverse event; T790M, EGFR Thr790Met mutation; TKI, tyrosine kinase inhibitor.

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(54.5%) treated with platinum-pemetrexed. The safety and efficacy results in this subanalysis are consistent with the results of the overall AURA3 study, and support the use of osimertinib in Japanese patients with *EGFR* T790M mutation-positive NSCLC whose disease has progressed following first-line *EGFR*-TKI treatment. (ClinicalTrials.gov trial registration no. NCT02151981.)

KEYWORDS

epidermal growth factor receptor, Japanese, mutation, non-small-cell lung cancer, tyrosine kinase

1 | INTRODUCTION

Epidermal growth factor receptor TKIs are established as the first line of treatment of patients with *EGFR*-mutated NSCLC.¹ However, resistance nearly always develops. Despite good response rates with first-line *EGFR*-TKIs, most patients experience disease progression within 8–14 months of treatment.^{1–3} A point mutation in the *EGFR* gene leading to T790M is found in approximately 50%–60% of *EGFR*-TKI-treated patients at the time of disease progression.^{4–7} This mutation is believed to render the receptor refractory to inhibition by reversible first-generation *EGFR* TKIs through effects on both steric hindrance⁸ and increased ATP affinity.⁹ Although afatinib, an irreversible second-generation *EGFR* TKI, overcame T790M activity preclinically,¹⁰ it failed to overcome T790M-mediated resistance in patients.^{11,12}

Two studies of Japanese individuals found that the prevalence of the *EGFR* T790M mutation was 50% and 64% in tumors with acquired resistance to *EGFR*-TKIs.^{13,14} A previous study showed a poor response to platinum-based doublet chemotherapy with or without bevacizumab in Japanese NSCLC patients with de novo and acquired *EGFR* T790M mutations, with overall response rates of 25.0% and 22.2% and median survival times of 29.1 and 15.3 months, respectively.¹⁵ After failure with first-line *EGFR*-TKI treatment in Japanese patients with *EGFR* mutation-positive advanced NSCLC, responses to platinum-based chemotherapy were poor, as shown by an ORR and median survival time of 25.4% and 28.9 months, respectively.¹⁶ A phase II study of NSCLC patients, including those with *EGFR* mutations, who experienced disease progression after erlotinib and/or gefitinib treatment also showed a poor response, with an ORR and median PFS of 8.2% and 4.4 months, respectively, after treatment with the irreversible ErbB family blocker, afatinib.¹² In the same study, the best response in 2 patients with acquired *EGFR* T790M mutations was stable disease.

Osimertinib is an oral, irreversible, CNS-penetrant *EGFR*-TKI with high selectivity for mutated *EGFR*, including *EGFR* with the T790M mutation.^{17,18} A phase I study of osimertinib found an overall ORR of 51% in patients who had progressed following prior treatment with *EGFR*-TKI inhibitors. The response rate was 61% in evaluable patients with confirmed *EGFR* T790M, and 21% in those without detectable *EGFR* T790M.¹⁹ The safety and efficacy of osimertinib 80 mg once daily were studied in a phase II, single-arm study in

patients previously treated with an *EGFR*-TKI. In the analysis of data from a phase II study in 199 patients, a complete objective response was obtained in 3% of patients, and partial responses in 67%, with manageable AEs.²⁰

AURA3 is an international, randomized (2:1), open-label, phase III clinical trial to compare the efficacy of osimertinib with that of platinum-based therapy plus pemetrexed.²¹ The trial enrolled 419 *EGFR* T790M mutation-positive patients with advanced NSCLC who had disease progression following first-line *EGFR*-TKI therapy. Approximately two-thirds of the patients were Asian. Compared with platinum therapy plus pemetrexed, median PFS was significantly increased with osimertinib treatment (hazard ratio, 0.30; 95% CI, 0.23–0.41; $P < 0.001$; 4.4 months vs. 10.1 months). Similarly, the ORR was significantly higher with osimertinib (71.1%) compared with platinum-based therapy plus pemetrexed (31%).²¹ This current subgroup analysis, prespecified in the statistical analysis plan of the AURA3 study, was designed to investigate the efficacy and safety of osimertinib in the Japanese patients enrolled in AURA3.

2 | MATERIALS AND METHODS

2.1 | Trial design

Patients were enrolled from 24 centers in Japan. The design of the study has been reported in detail elsewhere.²¹

In the overall cohort, patients were randomized in a 2:1 ratio to receive either osimertinib or pemetrexed plus either carboplatin or cisplatin (platinum-pemetrexed). Investigators chose either carboplatin or cisplatin for each patient before randomization. Patients were randomized centrally using an interactive voice/web response system. Sixty-three (15%) of the 419 participants enrolled in the original AURA3 study were recruited in Japan and were included in the current analysis.

All patients provided written informed consent prior to screening. Patients were free to discontinue treatment or to withdraw consent to participate in the study at any time. The study adhered to the principles laid down in the Declaration of Helsinki and relevant local and international guidelines and was approved by ethics committees or institutional review boards at all participating institutions. The study is registered at ClinicalTrials.gov (NCT02151981).

2.2 | Patients

Male and female patients aged ≥ 18 years (≥ 20 years in Japan) and who provided written informed consent were included. Specific inclusion criteria were as follows: (i) locally advanced or metastatic, histologically or cytologically documented NSCLC not amenable to surgery or radiotherapy; (ii) evidence of disease progression following first-line EGFR-TKI therapy; (iii) documented *EGFR* mutation and central confirmation of tumor *EGFR* T790M mutation from a tissue biopsy taken after disease progression following first-line EGFR-TKI treatment; (iv) WHO performance status of 0 or 1; (v) no more than 1 prior line of treatment for advanced NSCLC; and (vi) no prior neoadjuvant or adjuvant chemotherapy treatment in the 6 months preceding the first EGFR-TKI treatment. Patients with stable asymptomatic CNS metastases (defined as not requiring corticosteroids for 4 weeks before study treatment) were eligible for inclusion.

The exclusion criteria were as follows: (i) treatment with an approved EGFR-TKI within 8 days of the first dose of study treatment; (ii) prior treatment with osimertinib or any T790M-directed EGFR-TKI; (iii) prior use of investigational agents or anticancer drugs within 14 days of randomization; and (iv) inadequate bone marrow reserve or organ function.

2.3 | Interventions

This was an open-label study. In the osimertinib group, patients received oral osimertinib at a dose of 80 mg once daily. In the platinum-pemetrexed group, patients received i.v. pemetrexed 500 mg/m² plus either carboplatin at an area under the plasma concentration-time curve of 5, or cisplatin 75 mg/m² every 3 weeks for up to 6 cycles. Optional maintenance pemetrexed treatment was permitted for patients whose disease had not progressed after 4 cycles of platinum-pemetrexed.

Treatment continued until disease progression, the development of unacceptable AEs, or a request by either the patient or the physician to discontinue treatment. In accordance with a protocol amendment, patients assigned to platinum-pemetrexed could be switched to osimertinib in the event of disease progression assessed by the investigator and confirmed by a blinded independent central review committee.

2.4 | Outcomes

The primary outcome measure was PFS assessed by the investigator according to RECIST version 1.1. Analysis of PFS by a blinded independent central review committee was carried out as a sensitivity analysis. All patients had RECIST 1.1 assessments every 6 weeks until objective progression. Secondary outcome measures included overall survival, ORR, duration of response, DCR, tumor shrinkage, and safety and tolerability. Safety assessments included clinical chemistry, hematology and urinalysis, vital signs and physical examination, echocardiogram/multigated acquisition scan, and WHO

performance status. Adverse events were classified using the NCI's CTCAE version 4.0.

2.5 | Statistical analyses

A full description of the statistical analyses, including the sample size calculation, has been reported in detail elsewhere.²¹ The full analysis set included all randomized patients and was used for all efficacy and exploratory analyses. The safety analysis set comprised all patients who received at least 1 dose of randomized treatment. No statistical analyses were undertaken for safety data and they were presented as summary data. All calculations were carried out with SAS software version 9.4 (SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Patients

Patients were enrolled and randomized between August 2014 and September 2015. The tissue biopsy samples of 174 Japanese patients were screened by central testing for *EGFR* T790M mutations after progression, prior to study entry. Of the 111 patients excluded for not meeting eligibility criteria, *EGFR* T790M mutation was not confirmed in 97 patients. Sixty-three Japanese patients were randomized and received treatment (osimertinib, $n = 41$; and platinum-pemetrexed, $n = 22$). Fifteen out of 19 patients (78.9%) who discontinued randomized treatment in the platinum-pemetrexed arm at the data cut-off (15 April 2016) crossed over to the osimertinib arm. The patient disposition in the Japanese subgroup is shown in Figure 1.

Table 1 provides the characteristics of enrolled patients in the overall cohort and the Japanese subgroup. Patient characteristics in the Japanese subgroup were comparable with those in the overall study cohort. Baseline characteristics were generally balanced across treatment groups in the overall study cohort and in the Japanese subgroup. In the Japanese subgroup, 63.5% of patients were female ($n = 40$) and 65.1% were never-smokers ($n = 41$). The percentage of patients with CNS metastases at baseline was 30.2% ($n = 19$) in the Japanese subgroup (29.3% in the osimertinib group and 31.8% in the platinum-pemetrexed group; Table 1).

At the data cut-off, the median duration of treatment was 9.95 months (range, 0.6-17.5 months) for osimertinib and 5.03 months (range, 0.7-14.0 months) for platinum-pemetrexed. After disease progression, patients were treated with chemotherapy (platinum doublet, monotherapy), EGFR-TKIs, immune checkpoint inhibitors, or radiation therapy.

3.2 | Progression-free survival and tumor responses

Figure 2 shows PFS in the global cohort²¹ and Japanese subgroup. PFS was longer in the osimertinib group than in the platinum-pemetrexed group. In the Japanese subgroup, the hazard ratio was 0.27 (95% CI, 0.13-0.56), and the median PFS was 12.5 months in the

osimertinib group and 4.3 months in the platinum-pemetrexed group. These results were consistent with those in the global cohort. Table 2 shows a comparison of best objective responses, the ORR, DCR, and duration of response in the 2 treatment groups. The mean reduction of tumor size in the target lesion after 6 weeks was 34.7% in the osimertinib group and 18.8% in the platinum-pemetrexed group. All 41 patients in the osimertinib group showed a reduction of tumor size in the target lesion regardless of the best objective response (partial response, stable disease, or progressive disease). Among patients in the platinum-pemetrexed group, most (19/22, 86.4%) showed a reduction of tumor size in the target lesion, except for 3 patients (3/22, 13.6%) who showed an increase of tumor size in the target lesion (1 patient with stable disease and 2 patients with progressive disease) (Figure S1). The findings for secondary outcomes were broadly similar between the Japanese patients and the overall cohort. Overall survival was not analyzed because the data were immature at the cut-off.

3.3 | Safety

Adverse events occurred in all patients in both groups. Grade ≥ 3 AEs or SAEs were reported in a higher proportion of patients in the platinum-pemetrexed group (Table 3). Adverse events that were

determined as possibly related to treatment by investigators in the Japanese subgroup analysis (summarized in Table 4) occurred in 39 patients (95.1%) treated with osimertinib and 22 patients (100%) treated with platinum-pemetrexed. Paronychia, diarrhea, and skin events including dry skin, pruritus, and dermatitis acneiform were observed in higher proportions in the osimertinib group than in the platinum-pemetrexed group. Nausea, malaise, decreased appetite, anemia, constipation, decreased platelet count, decreased neutrophil count, decreased white blood cell count, increased alanine aminotransferase, increased aspartate aminotransferase, stomatitis, fatigue, and pyrexia were more frequent in the platinum-pemetrexed group than in the osimertinib group.

The CTCAE grade ≥ 3 AEs judged as possibly related to osimertinib included increased alanine aminotransferase, increased aspartate aminotransferase, diarrhea, and decreased appetite. Adverse events of CTCAE grade ≥ 3 were reported in 13 patients (31.7%) treated with osimertinib and in 15 patients (68.2%) treated with platinum-pemetrexed. Grade ≥ 3 AEs that were determined as possibly related to treatment by investigators occurred in 5 patients (12.2%) treated with osimertinib and 12 patients (54.5%) treated with platinum-pemetrexed. Adverse events causally related to treatment that led to treatment discontinuation occurred in 3 patients (7.3%) treated with osimertinib and 2

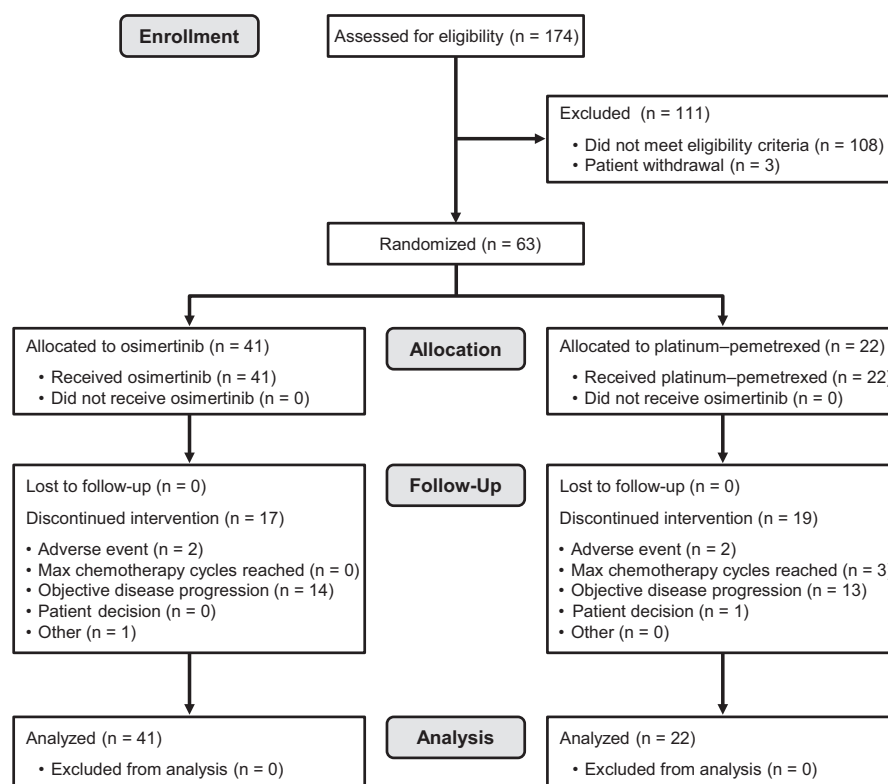


FIGURE 1 Patient disposition in the Japanese subgroup of patients with *EGFR* T790M mutation-positive advanced non-small-cell lung cancer treated with osimertinib or platinum-pemetrexed therapy. Patients in the platinum-pemetrexed group were counted only if they discontinued all platinum-pemetrexed treatment. If a patient discontinued platinum-pemetrexed treatments at different times during the trial, they were counted under the last recorded reason for discontinuation of platinum-pemetrexed. If a patient discontinued platinum-pemetrexed treatments at the same time, the patient was counted under a single reason using the following order: adverse event, objective disease progression, severe protocol non-compliance, lost to follow-up, patient decision, maximum cycle of platinum-pemetrexed reached, or other

TABLE 1 Demographic characteristics in the overall study cohort and Japanese subgroup of patients with *EGFR* T790M mutation-positive advanced non-small-cell lung cancer treated with osimertinib or platinum-pemetrexed

Characteristic	Osimertinib		Platinum-pemetrexed	
	All patients ²¹ (n = 279)	Japanese patients (n = 41)	All patients ²¹ (n = 140)	Japanese patients (n = 22)
Sex, %				
Male	38.4	36.6	30.7	36.4
Female	61.6	63.4	69.3	63.6
Age, years, median (range)	62.0 (25-85)	69 (25-85)	63.0 (20-90)	67 (33-90)
Race, %				
White	31.9	Japanese only	32.1	Japanese only
Asian	65.2		65.7	
Other ^a	2.8		2.1	
Smoking status, %				
Never	67.7	68.3	67.1	59.1
Current	5.0	14.6	5.7	13.6
Former	27.2	17.1	27.1	27.3
CNS metastases ^b , %	33.3	29.3	36.4	31.8
<i>EGFR</i> mutations ^c , %				
T790M ^d	98.6	97.6	98.6	100.0
Exdel19	68.5	56.1	62.1	72.7
L858R	29.7	39.0	32.1	27.3
Other ^e	2.2	4.8	3.5	0.0
Number of previous anticancer regimens, %				
1	96.4	95.1	95.7	100.0
2	3.2	4.9	4.3	0.0
3	0.4 ^f	0.0	0.0	0.0

Exdel19, exon 19 deletion; L858R, Leu858Arg mutation.

^aIncluding Black or African American and American Indian or Alaskan native.

^bCentral nervous system (CNS) metastases determined programmatically from baseline date of CNS lesion site, medical history and/or surgery, and/or radiotherapy.

^c*EGFR* mutation identified by Cobas *EGFR* mutation test (by biopsy taken after confirmed progression on most recent treatment regimen).

^dSix patients without centrally confirmed Thr790Met (T790M) mutation-positive status documented in the trial database/3 patients subsequently confirmed to be tumor T790M mutation-positive. In the Japanese subgroup, 1 patient in the osimertinib group was reported as having missing results, but was T790M mutation-positive (100% T790M positive, n = 63): the patient had a T790M positive result recorded under the patient's previous study code, which was missing from the database by error.

^eIncludes G719X, S768I, and exon 20 insertion.

^fOne patient had 3 previous anticancer regimens.

patients (9.1%) treated with platinum-pemetrexed. In the osimertinib group, these were ILD-like AEs (1 patient with grade 1 pneumonitis and 2 patients with grade 2 ILD). Grade 2 events of QT prolongation were reported in 1 patient (2.4%) treated with osimertinib and 1 patient (4.5%) treated with platinum-pemetrexed (Table 4).

Serious AEs were less common in the osimertinib group than the platinum-pemetrexed group (5 patients [12.2%] vs. 6 patients [27.3%], respectively). One Japanese patient, whose events were considered possibly related to study treatment by the investigator, developed interstitial pneumonitis almost 7 months after starting treatment, and treatment was discontinued. Nine days later, pneumothorax was reported but the patient subsequently recovered. In total, 4 (9.8%) patients in the osimertinib group and 5 (22.7%) patients in the platinum-pemetrexed group died, including those who

died during the crossover period or after the follow-up period. All 9 deaths, including all 4 in the osimertinib group, were considered related to the disease under investigation. No fatal SAE was reported in the Japanese subgroup.

4 | DISCUSSION

The objective of the current study was to evaluate the safety and efficacy of osimertinib in the 63 Japanese patients enrolled in AURA3. This was a randomized, open-label, phase III clinical trial of NSCLC patients with the *EGFR* T790M mutation whose disease progressed after first-line *EGFR*-TKI treatment.

Our findings in the Japanese subgroup are consistent with those for the overall study cohort.²¹ Clinically relevant improvements were

observed in PFS and tumor responses in the osimertinib group compared with the platinum-pemetrexed group of the Japanese subgroup (hazard ratio, 0.27; 95% CI, 0.13-0.56). The median PFS was 12.5 months in the osimertinib group and 4.3 months in the platinum-pemetrexed group.

Our results were similar to a previous Japanese phase III study in patients with advanced *EGFR*-mutated NSCLC who were naïve to any *EGFR*-TKIs and were randomized to treatment with another *EGFR*-TKI treatment, gefitinib, or chemotherapy, although the target patients were TKI-pretreated *EGFR* T790M mutation-positive in this AURA3 study,² which reported a significantly longer PFS with gefitinib than chemotherapy (10.4 months vs. 5.5 months, respectively;

hazard ratio for PFS with gefitinib, 0.36; 95% CI, 0.25-0.51; $P < 0.001$). This indicated that the use of osimertinib in patients harboring the *EGFR* T790M mutation after disease progression by prior *EGFR*-TKI therapy is supported even in the Japanese population. Notably, among 174 Japanese and 1036 overall patients screened, 63 (36.2%) and 413 (39.9%) patients, respectively, were enrolled in the study with T790M mutation-positive status.²¹ Thus, the proportion of patients with documented *EGFR* T790M mutation between the Japanese and global cohorts was broadly similar.

Treatment options for NSCLC patients with *EGFR* mutations who experienced disease progression after *EGFR*-TKI therapy are limited. The LUX-Lung 1 and LUX-Lung 4 trials evaluated the efficacy of afatinib in NSCLC patients after failure with erlotinib or gefitinib in a global study cohort and Japanese patients, respectively.^{11,12} In these studies, only a small portion of the patients possessed *EGFR* T790M mutations. The PFS ranged between 3 and 4 months, ORR ranged between 7% and 8%, and no clinically significant response was found.

The IMPRESS trial evaluated the efficacy and safety of continuing gefitinib combined with chemotherapy vs chemotherapy alone in patients with *EGFR* mutation-positive advanced NSCLC with acquired resistance to first-line gefitinib. The median PFS and ORR for the pemetrexed plus carboplatin/cisplatin regimen in the

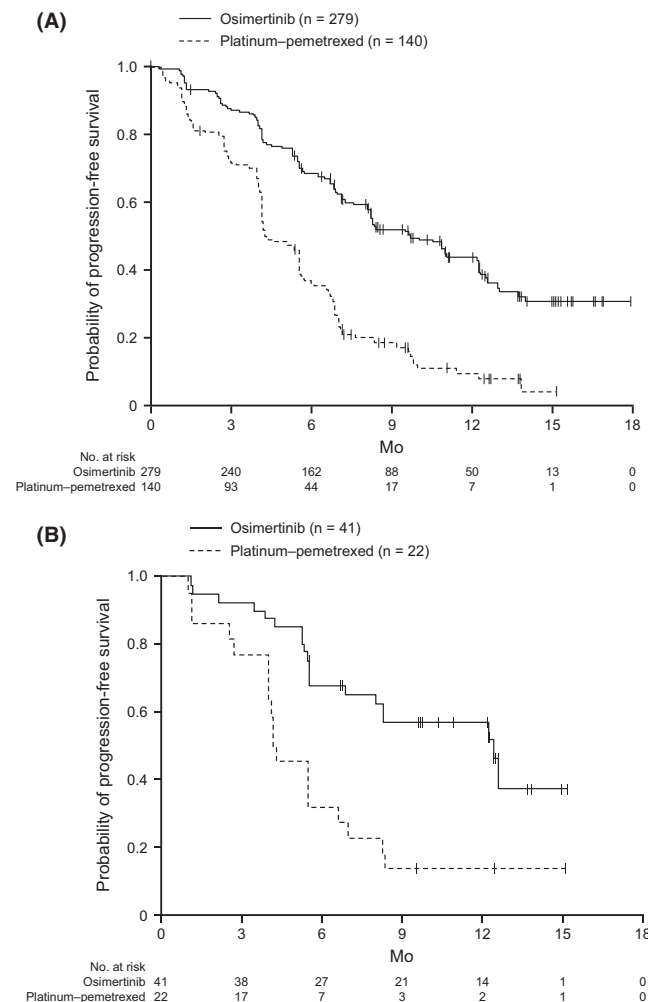


FIGURE 2 Progression-free survival (PFS) using investigator assessment in all patients²¹ (A) and Japanese patients (B) enrolled with *EGFR* T790M mutation-positive advanced non-small-cell lung cancer treated with either osimertinib or platinum-pemetrexed therapy. A, In all patients, the median PFS was 10.1 mo (95% confidence interval [CI], 8.3-12.3) in the osimertinib group and 4.4 (95% CI, 4.2-5.6) in the platinum-pemetrexed group (hazard ratio, 0.30; 95% CI, 0.23-0.41; $P < 0.001$). B, In the Japanese patients, the median PFS was 12.5 mo (95% CI, 6.9-not calculated) in the osimertinib group and 4.3 (95% CI, 4.0-6.7) in the platinum-pemetrexed group (hazard ratio, 0.27; 95% CI, 0.13-0.56)

TABLE 2 Tumor response in the Japanese subgroup of patients with *EGFR* T790M mutation-positive advanced non-small-cell lung cancer treated with osimertinib or platinum-pemetrexed

	Osimertinib (n = 41)	Platinum- pemetrexed (n = 22)
Best objective response, n (%)		
Complete response	0 (0.0)	0 (0.0)
Partial response	29 (70.7)	8 (36.4)
Non-response (total)	12 (29.3)	14 (63.6)
Stable disease ≥ 6 wk	10 (24.4)	11 (50.0)
Progression	2 (4.9)	3 (13.6)
RECIST progression	2 (4.9)	2 (9.1)
Death	0 (0.0)	1 (4.5)
Objective response rate (%) ^a	70.7	36.4
Disease control rate (%) ^b	95.1	86.4
Duration of response, median no. of months (95% CI) ^c	11.1 (6.5-NC)	4.1 (1.5-7.1)
Patients remaining in response, n (%)		
>3 mo	26 (89.7)	5 (62.5)
>6 mo	19 (65.5)	2 (25.0)
>9 mo	11 (37.9)	1 (12.5)
>12 mo	2 (6.9)	1 (12.5)

NC, not calculated.

^aOdds ratio, 4.23 (95% confidence interval [CI], 1.45-13.23).

^bOdds ratio, 3.08 (95% CI, 0.47-24.89).

^cFrom onset of response.

TABLE 3 Rates of adverse events (AEs) in the overall study cohort and Japanese subgroup of patients with *EGFR* T790M mutation-positive advanced non-small-cell lung cancer treated with osimertinib or platinum-pemetrexed

	Osimertinib		Platinum-pemetrexed	
	All patients ²¹ (n = 279)	Japanese patients (n = 41)	All patients ²¹ (n = 136)	Japanese patients (n = 22)
AE, any ^a , n (%)				
Any AE	273 (97.8)	41 (100.0)	135 (99.3)	22 (100.0)
Any AE grade ≥3	63 (22.6)	13 (31.7)	64 (47.1)	15 (68.2)
Any AE leading to death	4 (1.4)	0 (0.0)	1 (0.7)	0 (0.0)
Any serious AE	50 (17.9)	5 (12.2)	35 (25.7)	6 (27.3)
Any AE leading to discontinuation	19 (6.8)	3 (7.3)	14 (10.3)	2 (9.1)
AE, possibly causally related, n (%)				
Any AE	231 (82.8)	39 (95.1)	121 (89.0)	22 (100)
Any AE grade ≥3	16 (5.7)	5 (12.2)	46 (33.8)	12 (54.5)
Any AE leading to death	1 (0.4)	0 (0.0)	1 (0.7)	0 (0.0)
Any serious AE	8 (2.9)	1 (2.4)	17 (12.5)	5 (22.7)
Any AE leading to discontinuation	10 (3.6)	3 (7.3)	12 (8.8)	2 (9.1)

Safety analysis set (all patients who received at least 1 dose of the study drug and for whom post-dose data were available). Adverse events were assessed by the investigator, and include those with an onset date on or after the date of the first dose and up to and including 28 days following the date of the last dose of study medication.

^aPatients with multiple events in the same category were only counted once in that category. Those with events in more than 1 category were counted once in each category.

IMPRESS trial were 5.4 months (95% CI, 4.6-5.5) and 34%, respectively.²² Thus, the median PFS and ORR in the AURA3 trial is considered to be broadly similar to the historical data. However, these comparisons should be interpreted with caution as there is no specific study of platinum doublet chemotherapy in patients with T790M mutation-positive NSCLC who have progressed on prior *EGFR*-TKI therapy, and the trials compared here are heterogeneous.

A retrospective analysis of 24 patients treated with *EGFR*-TKI rechallenge in combination with bevacizumab showed a higher DCR (88%) and a slightly longer PFS (4.1 months) than have previously been published for similar patients treated with *EGFR*-TKI rechallenge alone. Furthermore, both the DCR and PFS in this study were higher in *EGFR* T790M mutation-negative patients compared with those in *EGFR* T790M mutation-positive patients (DCR 88% vs. 86% [*P* = 1.00] and PFS 4.1 vs. 3.3 months [*P* = 0.048], respectively).²³ Although the present study showed clinically meaningful improvement in PFS in the osimertinib group vs the platinum-pemetrexed group, further study is warranted to determine whether combination treatment with anti-vascular endothelial growth factor therapy would provide any additional benefit, particularly in *EGFR* T790M mutation-positive patients.

In the current study, there were small numerical differences in AEs in the osimertinib group compared with the overall study cohort (22%).²¹ However, the safety profile of osimertinib in the Japanese patients was broadly similar to the overall cohort and no new safety signals were presently identified. Three Japanese patients in the osimertinib group experienced 3 ILD-related AEs (CTCAE grades 1 and 2), and all 3 patients recovered. There was no increase in ILD

severity in the Japanese subgroup compared with the overall study cohort.

This study has some limitations, including its open-label nature.²¹ Given that this was a subgroup analysis, the number of patients is relatively small, meaning results should be interpreted with some caution.

In conclusion, the results of this study suggest that osimertinib is effective as a standard regimen in Japanese NSCLC patients carrying the *EGFR* T790M mutation with disease progression after *EGFR*-TKI therapy. Osimertinib was relatively well tolerated, with low incidences of causally related AEs classified as CTCAE grade ≥3 or SAEs. The findings in this subgroup of Japanese patients were consistent with those observed in the overall study cohort.

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TABLE 4 Possibly causally related adverse events (AEs) in the Japanese subgroup of patients with EGFR T790M mutation-positive advanced non-small-cell lung cancer treated with osimertinib or platinum-pemetrexed

	Osimertinib (n = 41)		Platinum-pemetrexed (n = 22)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
All AEs >15%, n (%)				
Any AE	39 (95.1)	5 (12.2)	22 (100)	12 (54.5)
Paronychia	18 (43.9)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	14 (34.1)	1 (2.4)	2 (9.1)	0 (0.0)
Dry skin	8 (19.5)	0 (0.0)	1 (4.5)	0 (0.0)
Stomatitis	7 (17.1)	0 (0.0)	7 (31.8)	0 (0.0)
Pruritus	7 (17.1)	0 (0.0)	1 (4.5)	0 (0.0)
Dermatitis acneiform	6 (14.6)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	2 (4.9)	0 (0.0)	14 (63.6)	0 (0.0)
Malaise	0 (0.0)	0 (0.0)	12 (54.5)	0 (0.0)
Decreased appetite	2 (4.9)	1 (2.4)	11 (50.0)	4 (18.2)
Anemia	2 (4.9)	0 (0.0)	10 (45.5)	4 (18.2)
Constipation	1 (2.4)	0 (0.0)	10 (45.5)	0 (0.0)
Platelet count decreased	4 (9.8)	0 (0.0)	7 (31.8)	3 (13.6)
Neutrophil count decreased	3 (7.3)	0 (0.0)	7 (31.8)	4 (18.2)
White blood cell count decreased	5 (12.2)	0 (0.0)	5 (22.7)	2 (9.1)
Alanine aminotransferase increased	5 (12.2)	2 (4.9)	4 (18.2)	0 (0.0)
Fatigue	1 (2.4)	0 (0.0)	4 (18.2)	0 (0.0)
Aspartate aminotransferase increased	5 (12.2)	2 (4.9)	4 (18.2)	0 (0.0)
Pyrexia	0 (0.0)	0 (0.0)	4 (18.2)	0 (0.0)
Select adverse events <15%, n (%)				
Interstitial lung disease ^a	3 (7.3)	0 (0.0)	0 (0.0)	0 (0.0)
QT prolongation	1 (2.4)	0 (0.0)	1 (4.5)	0 (0.0)

Safety analysis set (all patients who received at least 1 dose of the study drug and for whom post-dose data were available). Adverse events were assessed by the investigator, and include those with an onset date on or after the date of the first dose and up to and including 28 days following discontinuation of randomized treatment or the day before first administration of cross-over treatment if within 28 days. Some patients had more than 1 AE.

^aGrouped term: if a patient had multiple preferred term level events within a specific grouped term AE, then the maximum grade of CTCAE across those events was counted.


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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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